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J. Am. Chem. Soc., **2007**, 129 (46), 14190-14192• DOI: 10.1021/ja0760426 • Publication Date (Web): 25 October 2007

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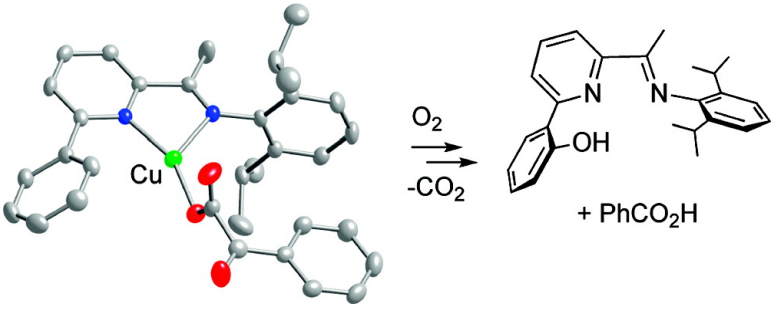

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Published on Web 10/25/2007

Copper(I)−α-Ketocarboxylate Complexes: Characterization and O_2 Reactions That Yield Copper−Oxygen Intermediates Capable of Hydroxylating Arenes

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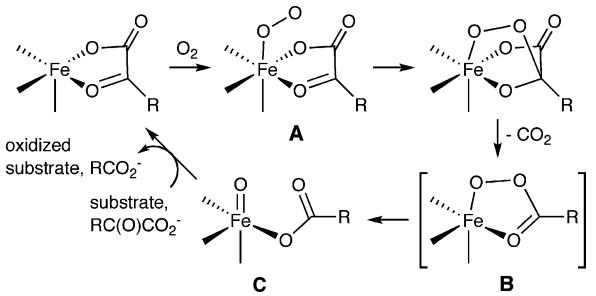
Understanding the properties of synthetic copper−oxygen intermediates is important for evaluating mechanisms of oxidations by enzymes and other catalysts.[1,2] A growing class of reactive copper−oxygen complexes have been isolated or identified spectroscopically to date, including well-studied examples with $[Cu_2(O_2)]^{2+}$, $[Cu_2(\mu\text{-}O)_2]^{2+}$, or $[CuO_2]^+$ cores.[3] Mononuclear copper−oxo species ($[Cu^{II}-O^{-\bullet} \leftrightarrow Cu^{III}{=}O^{2-}]^+$) are less well understood. Such species have been considered as a possible reactive intermediate in catalysis by copper enzymes (cf. peptidylglycine α-hydroxylating monooxygenase,[4,5] particulate methane monooxygenase[6]) and in some synthetic reactions,[7] but to our knowledge, they have only been observed in the gas phase.[8] Theory suggests that they should be powerful oxidants,[4,8,9] perhaps even more reactive than the related $[Fe^{IV}{=}O]^{2+}$ unit that has been extensively studied.[10] Among the various routes by which $[Fe^{IV}{=}O]^{2+}$ moieties may be accessed is that used by α-ketoglutarate-dependent non-heme iron enzymes (Scheme 1).[11] Experimental and theoretical studies[12] support a mechanism that involves reaction of O_2 with a bidentate α-ketocarboxylate complex of Fe^{II} to yield an O_2 adduct (**A**) that attacks the α-keto position to induce loss of CO_2 and generate **B**. Formally a Fe^{II}−OOC(O)R species, **B**, then undergoes O−O bond heterolysis to yield the $[Fe^{IV}{=}O]^{2+}$ moiety (**C**) that is generally deemed to be responsible for attacking the C−H bond of the substrate(s).

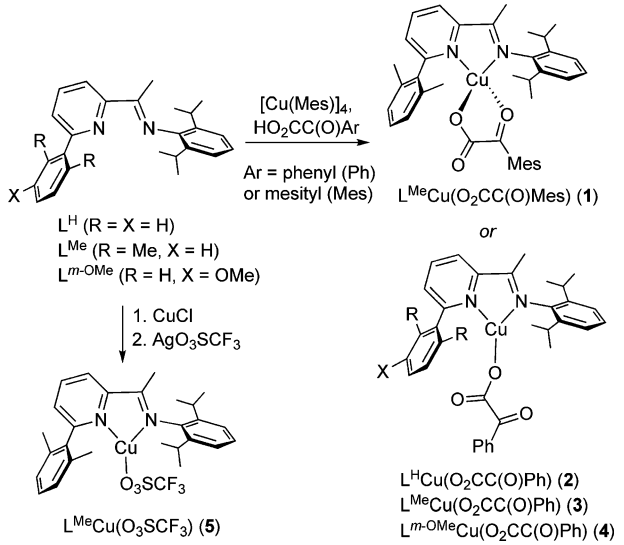
Drawing an analogy to this chemistry, we envisioned that reaction of O_2 with a Cu^I−α-ketocarboxylate could similarly generate novel $[Cu^I-OOC(O)R]$ and/or derived $[Cu^{II}-O^{-\bullet} \leftrightarrow Cu^{III}{=}O^{2-}]^+$ species. In view of their potentially high reactivity that could make these species difficult to observe directly, we postulated that they might be trapped by using a supporting ligand with an arene substituent appropriately positioned to be susceptible to intramolecular attack.[13,14] Herein we report the synthesis and structural characterization of new Cu^I−α-ketocarboxylate complexes with such ligands, the discovery of decarboxylation and arene hydroxylation upon reaction of these complexes with O_2, and theoretical calculations that provide provocative mechanistic insights into the reactions. These findings serve to illustrate a new pathway for the generation of novel copper−oxygen intermediates relevant to oxidation catalysis.

Using modifications of known methods,[15] we prepared bidentate L^H,[16] L^{Me}, and L^{m-OMe} (Scheme 2), which were chosen because they would favor low coordination numbers in their complexes, provide a single appended arene in a position suited for intramolecular oxidation,[7d,13,14,17] and contain a sterically bulky 2,6-diisopropylphenyl group to inhibit formation of bis-ligand complexes (e.g., L_2Cu^+) and dicopper−oxygen intermediates.[3] Copper(I)−α-ketocarboxylate complexes **1**−**4** were synthesized by treatment of $[Cu(Mes)]_4$ with benzoyl or mesitoyl formic acid, followed by addition of the N-donor ligand. For comparative O_2 reactivity studies

Scheme 1. General Mechanism for Reactivity of Fe^{II}−α-Ketocarboxylate Sites in Enzymes and Model Complexes



Scheme 2. Synthesis of Copper(I) Complexes



(see below), we also prepared **5** by treating L^{Me} with CuCl and then AgO_3SCF_3. The compounds **1**−**5** were isolated as red-brown (**1**−**4**) or purple (**5**) solids in good yields (∼75−85%) and were fully characterized by NMR and UV−vis spectroscopy, CHN analysis, and X-ray crystallography.[15]

The structures of **1** and **2** are shown in Figure 1, while those of **3**−**5** appear in the Supporting Information (Figures S1−S3). The α-ketocarboxylate coordinates in chelating bidentate fashion via the carboxylate and the ketone O atoms in **1**, but in **2**−**4**, it binds solely through a carboxylate O atom with the keto group oriented approximately orthogonal to the carboxylate plane (torsional angle O1−C26−C27−O3 = −103.5(3)°). In **5**, the triflate anion binds as a monodentate ligand to yield a three-coordinate complex. All structures display metal−ligand bond distances typical for Cu^I complexes. For **1**−**4**, similar ^1H and $^{13}C\{^1H\}$ NMR spectra are

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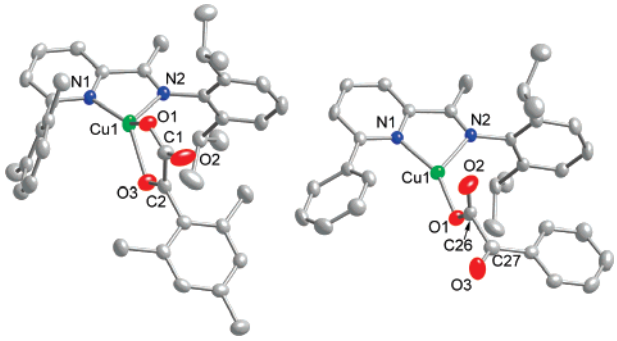
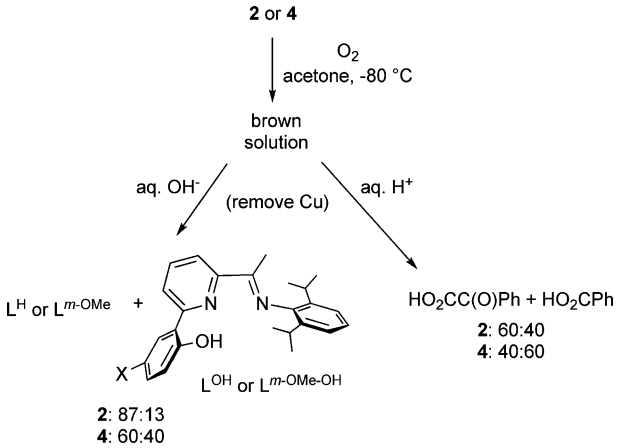


Figure 1. Representations of the X-ray structures of **1** (left) and **2** (right) as 50% thermal ellipsoids, and hydrogen atoms are omitted for clarity. Selected interatomic distances (Å) and angles (deg) are as follows. **1**: Cu1−N1, 1.9676(19); Cu1−O1, 1.9904(19); Cu1−N2, 2.107(2); Cu1−O3, 2.1815(19); O1−C1, 1.261(3); C2−O3, 1.223(3); C2−C1, 1.545(3); O2−C1, 1.230(3); N1−Cu1−O1, 137.52(8); N1−Cu1−N2, 79.99(8); O1−Cu1−N2, 115.31(8); N1−Cu1−O3, 134.09(8); O1−Cu1−O3, 79.18(7); N2−Cu1−O3, 112.07(8). **2**: Cu1−O1, 1.9042(16); Cu1−N1, 1.9831(19); Cu1−N2, 2.1113(19); Cu1−O2, 2.888(2); C26−O2, 1.216(3); C26−O1, 1.279(3); C26−C27, 1.529(3); O3−C27, 1.216(3); O1−Cu1−N1, 154.80(8); O1−Cu1−N2, 123.60(8); N1−Cu1−N2, 80.74(7); O2−C26−O1, 127.2(2).

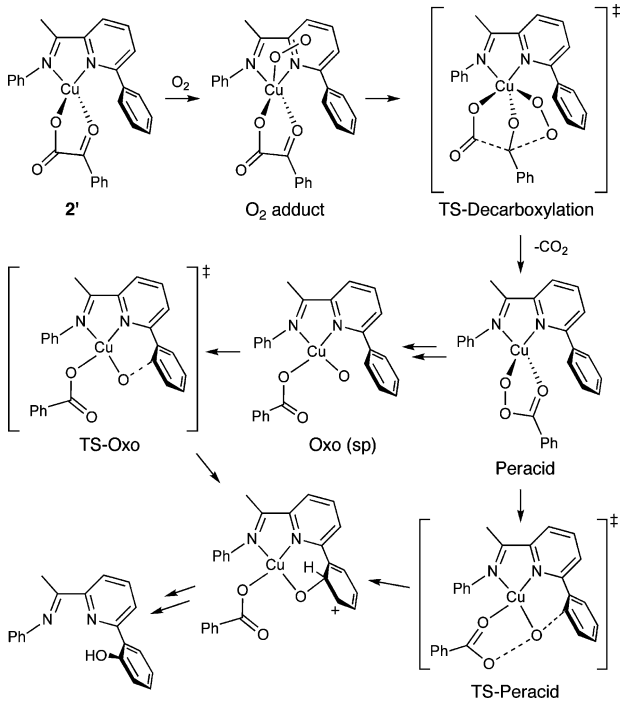
Scheme 3. Reactivity of **2** and **4** with O_2



observed in CD_2Cl_2 at ambient temperature which exhibit a single set of sharp peaks, indicating that in solution they either retain the structures observed by X-ray diffraction or undergo fluxional processes that are sufficiently rapid to result in an averaged spectrum (cf. bidentate/monodentate α-ketocarboxylate isomerization).[15] Density functional calculations at the M06L level[18] on model systems with unsubstituted aryl rings (hereafter **2′**) found local minima having both monodentate and bidentate coordination of the ketoacid to copper, with the latter preferred by about 7 kcal/mol.

Exposure of solutions of **2** or **4** to O_2 in acetone at −80 °C resulted in gradual (∼2−4 h) formation of brown solutions. After warming and removal of copper under basic conditions, a mixture of unperturbed ligand (L^H or L^{m-OMe}) and hydroxylated versions (L^{OH} or $L^{m-OMe-OH}$) was identified by ^1H NMR spectroscopy (>95% recovery, ratios indicated in Scheme 3). Acidic workup led to the isolation (>98% recovery, NMR) of benzoyl formic acid and benzoic acid (Scheme 3). The different extents of formation of the hydroxylated ligand and benzoic acid for **2** versus **4** indicate differing extents of decarboxylation and more efficient arene hydroxylation for **4**, which contains the more electron-rich arene group that would be expected to more rapidly trap an electrophilic copper−oxygen species. For the reaction of **4**, positive ion ESI-MS data were acquired on the crude brown reaction solution and the recovered ligand residue. Intense peaks with correct *m/z* and isotope patterns for $[(L^{m-OMe-O})_2Cu_2(benzoate)]^+$ and $[L^{m-OMe-O}Cu]^+$

Scheme 4. Calculated Mechanisms for O_2-Induced Decarboxylation and Arene Substituent Hydroxylation of Model **2′**



for the reaction solution and $[L^{m-OMe-OH} + X^+]$ (X = H or Na) for the ligand residue were observed. Critically, when $^{18}O_2$ was used, the ESI-MS data for these species showed that one ^{18}O atom was incorporated into the ligand and one into the benzoate,[15] consistent with expectation for a reaction pathway akin to that drawn for Fe in Scheme 1.[19]

Computed mechanisms at the M06L density functional level and including singlet-state energy corrections based on CASPT2 calculations for the reaction of model system **2′** with oxygen are shown in Scheme 4 and, more fully, Figures S11 and S12.[18] Addition of O_2 delivers a complex ("O_2 adduct") that adopts either of two energetically similar structures: a singlet structure with a side-on bound O_2 fragment, analogous in character to Cu(III)−peroxo species supported by diketiminate ligands,[3e] or a triplet state featuring end-on O_2 coordination (shown). After migration of one O atom of the O_2 fragment to the ketocarbon of the ketoacid, loss of CO_2 to generate a singlet Cu(I)−peracid complex ("Peracid") is predicted to occur with a gas-phase free energy of activation of 15.4 kcal/mol. Decarboxylation is predicted overall to be exergonic by about 34 kcal/mol.

Two pathways leading to oxygenation of the 2-pyridyl benzene ring from this peracid complex were characterized. In the first, a singlet transition-state structure involving oxidation of the ligand by the peracid itself was located ("TS-Peracid"); this structure features O−O and O−C bond distances of 2.47 and 2.38 Å, respectively, and a Cu−O bond distance of 1.72 Å, so it appears very "oxo-like" in character. In the second pathway, initial cleavage of the peracid O−O bond led to a stable trigonal bipyramidal copper−oxo intermediate (shown in Figure S11), which isomerizes to a square planar isomer ("Oxo (sp)"), both of which are best described as triplet Cu(II) oxyl species.[1e,8] The square planar intermediate is the reactive species in the hydroxylation reaction, which proceeds through a triplet transition-state structure ("TS-Oxo") having Cu−O and O−C bond lengths of 1.84 and 1.93 Å, respectively. Computationally, both paths lead to the same triplet oxygenated cyclohexadienyl cation product, with the latter pathways predicted to be more accessible than the former (highest activation

free energies of 10.4 and 17.8 kcal/mol relative to the peracid intermediate, respectively).[18] We note, however, that additional kinetic constraints associated with spin crossings between the singlet and triplet surfaces may permit either or both pathways to contribute to the observed reactivity. Such crossings have been noted in prior studies of Cu(II) oxyl reactivity[8] and α-ketoglutarate-dependent non-heme iron reactivity,[12] and their general relevance to iron-based oxidations has been demonstrated.[10d−g] Accounting for spin-crossing barriers within the context of transition-state theory has been discussed,[20] and while a detailed kinetic analysis of this effect is of interest, it goes beyond the scope of this communication. [We note that we have computed the relevant spin−orbit coupling matrix elements between the singlet and triplet states for the two TS structures originating from the singlet peracid intermediate. They have values of about 350 cm^{-1} in each case; values of this magnitude indicate that spin crossing should be reasonably efficient along either of the two paths.]

In summary, a series of copper(I)−α-ketocarboxylate complexes have been prepared and shown to exhibit variable coordination modes of the α-ketocarboxylate ligand. Reaction with O_2 induces decarboxylation of this ligand, and the derived copper−oxygen intermediate(s) has(have) been intercepted, resulting in hydroxylation of an arene substituent on the supporting N-donor ligand. The results show that the oxidative decarboxylation pathway for substrate oxidations by iron(II)−α-ketocarboxylate species in enzymes and model complexes[11,12] can be extended to copper analogues. Theoretical calculations have yielded intriguing mechanistic notions for the process, notably implicating hydroxylation pathways that involve novel $[Cu^{I}-OOC(O)R]$ and $[Cu^{II}-O^{-\bullet} \leftrightarrow Cu^{III}{=}O^{2-}]^{+}$ species. Future research will focus on identifying these species experimentally, using them to oxidize exogenous substrates, and differentiating between the postulated hydroxylation reaction pathways using theoretical and experimental methods.

Acknowledgment. We thank the National Institutes of Health (GM47365 to W.B.T.), the National Science Foundation (CHE06-10183 to C.J.C.), the Swiss National Science Foundation (200021-111645/1 to L.G.), and the DAAD (fellowship to S.M.H.) for financial support of this research.

Supporting Information Available: Full details of experimental and calculation procedures, characterization data, spectra, X-ray structure drawings of **3**−**5**, calculated reaction mechanism and coordinates (PDF), and X-ray crystallographic information (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0760426